BIOMARKERS FOR A SYSTEMIC LUPUS ERYTHEMATOSUS (SLE) DISEASE ACTIVITY IMMUNE INDEX THAT CHARACTERIZES DISEASE ACTIVITY

STATEMENT OF FEDERALLY FUNDED RESEARCH

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TECHNICAL FIELD OF THE INVENTION

[0002] The present invention relates in general to the field of biomarkers for calculating a lupus disease activity immune index that characterizes disease activity in Systemic Lupus Erythematosus (SLE).

REFERENCE TO A SEQUENCE LISTING

[0003] Not applicable.

BACKGROUND OF THE INVENTION

[0004] Without limiting the scope of the invention, its background is described in connection with Systemic Lupus Erythematosus (SLE).

[0005] Systemic autoimmune diseases, including SLE, afflict a significant proportion of the US population. Recent population-based studies reflect a prevalence of $^{73}/_{100,000}$ (1, 2), while the Lupus Foundation of America estimates the number of possible SLE patients to be as high as $^{470}/_{100,000}$ in routine clinical practice. SLE presents with a constellation of clinical symptoms; disease classification is contingent on meeting 4 of 11 American College of Rheumatology (ACR) criteria (3, 4). More than 90% of affected patients are women age 15-45. Prevalence is higher in minority populations and with lower socioeconomic status (5). Persistently active clinical disease and its treatment place patients at risk for organ damage (6-8), including central nervous system, pulmonary, cardiovascular, and renal damage (912), lupus nephritis, and end-stage renal disease (11, 13). Patients with waxing/waning disease and clinically active or quiescent disease are each at risk of clinical disease flare (14, 15).

[0006] SLE is a clinically and serologically heterogeneous systemic autoimmune disease that causes significant morbidity and early mortality, especially in young women and minorities Immune dysregulation in the form of pathogenic autoantibodies and chronic inflammation contributes to a wide range of clinical manifestations, including skin rashes, arthritis, and life-threatening renal and/or central nervous system damage. A number of antinuclear autoantibody (ANA) specificities have been shown to accumulate in SLE patients; use of hydroxychloroquine may abrogate autoantibody accumulation and offset clinical disease activity. Early intervention is an attractive approach to SLE treatment. However, our understanding of pathogenic mechanisms in SLE disease activity is inadequate. Closing this knowledge gap would improve our ability to identify individuals at risk of increased disease activity and permanent organ damage, define windows of opportunity for early intervention, and facilitate the development of pathway-targeted treatments.

[0007] Recognition and early treatment to prevent tissue and organ damage is challenging, as signs and symptoms of high disease activity are captured after their occurrence. Despite validated clinical disease activity instruments (16-18) and improved treatment strategies, persistently active disease remains a burden for SLE patients (19). Increased morbidity and early mortality associated with treatment required to manage active disease, in particular steroids (20-23), as well as permanent organ damage (24, 25), including renal damage (26), further escalates costs. In addition, long-term use of steroids (23) and other immune-suppressants (27) required to manage disease activity are associated with increased morbidity. The inability to proactively manage clinical disease limits medical care to reactive treatment, precluding proactive strategies of adding or increasing steroid-sparing immune modifying agents (28) to prevent end-organ damage (6-8) and reduce the pathogenic and socioeconomic burdens of SLE (29).

[0008] Current biomarkers in SLE have limited utility for forecasting permanent organ damage. Although SLE-associated autoantibody specificities such as anti-dsDNA, anti-spliceosome and anti-Ro/SSA, accumulate in SLE patients, their presence is not sufficient to predict persistent active disease and progression to permanent organ damage. ANAs are also found in sera from patients with other systemic rheumatic diseases, and from healthy individuals who do not go on to develop SLE, including some unaffected family members of SLE patients, and up to 14% of the general population. Because individuals may remain healthy despite being ANA-positive, ANA positivity alone is likely not the sole pathogenic driver of SLE. In addition to ANA positivity, the dysregulation of various immune pathways driven by soluble mediators may contribute to the development of clinical disease. No single factor or mechanism is likely sufficient to explain the complexity and heterogeneity of SLE pathogenesis; thus a multivariate, longitudinal approach is warranted to delineate mechanisms of early disease pathogenesis and discern unique parameters that forecast SLE classification.

[0009] Despite clinical trials of a number of directed immune pathway treatments, including the first FDA-approved drug for SLE in over 50 years, Belimumab (30), the vast majority of these studies fail, in part due to lack of understanding the immune pathways dysregulated in a given patient. The need for immune-informed bio-markers as surrogate endpoints for clinical disease activity is becoming more pressing. Administrative burden limits the use of validated SLE clinical disease activity measures in routine practice (31). Validated disease activity instruments, such as the currently used hybrid Systemic Lupus Erythematosus Disease Activity Index (hSLEDAI) (32, 33) and the British Isles Lupus Assessment Group (BILAG) index (17), are labor intensive and require ongoing, specialized training as these clinical instruments are updated (34). Relying solely on physician experience to assess clinical disease activity carries the risk of unwanted variability and negative outcomes (31, 35).

[0010] Clinical heterogeneity in SLE underlies the scientific premise that: heterogeneic immune dysregulation underlies clinical disease activity. The inventors have previously shown that patients exhibit immune dysregulation prior to the onset of clinical SLE, amplified in a feed-forward mechanism as patients suffer tissue damage, develop clinical sequelae, and ultimately reach disease classification (36, 37). The inventors also described the accumulation of multiple SLE-associated autoantibodies (Au-